

ERP

Research Focus

Introduction

In the research focus that follows, some priorities and specific requests for application are presented. While currently important research problems are suggested, the focus is by no means exhaustive. Any proposal that is consistent with the purpose of the external research program will be considered.

The research needs are presented within the scientific areas of **Exposure/Biomarkers/Dosimetry, Epidemiological Research, Clinical and Model Systems Research, and Tobacco Smoke and Smoking Behavior**. Due to the interdisciplinary nature of research in these areas, many projects will encompass more than one of these areas. Therefore, interdepartmental collaborations and creative, innovative joint projects are encouraged whenever they serve to strengthen the quality of the experimental design or to enhance the interpretation and evaluation of results.

Exposure/Biomarkers/Dosimetry

Exposure assessment is a necessary component in the design of reliable studies to determine health consequences of exposures. The objective of exposure assessment is to determine qualitatively and quantitatively the exposure and dose of a specific chemical or complex mixture of chemicals to a test subject or population. Accurate estimates of exposure and dose are critical factors in the conduct of all types of health research including epidemiological, clinical, and model systems research which employ a variety of test subjects (humans, animal models, tissues, cells) and dose targets (organs, tissues, cells, molecules).

Exposure estimates classically are obtained from self-reports, area and personal monitoring, and biological monitoring with biomarkers. In epidemiological studies, accurate exposure estimates reduce bias and uncertainty and, in clinical and model systems studies, improve the reliability of dose-response data. Biomarkers may be useful in assessing exposure as well as effects (i.e., providing information about the biological activities and their role from exposure of target sites to health endpoint effects).

Applications are requested for the study of

- Measures of exposure, including methodologies, and
- Measures of biological effect, including metabolites of or adducts formed by the species of interest.

scope = range of specific
focus = concentration of attention

Experimental designs incorporating the use of biomarkers for the distributional analysis of exposure and effects in populations are encouraged.

Recent advances in the study of genomic and proteomic markers point to potential future successes. Research in this area includes:

- Development of assays for detection of markers of exposure, effect, and susceptibility,
- Development of valid models for dose prediction and extrapolation,
- Development of sensitive, specific biomarkers to study injury.

Epidemiological Research

Epidemiology is the scientific study of health-related events in human populations, and the application of this study to the control of health problems. Epidemiological research deals with the study of mortality - death and its causes, and the study of morbidity - illness and its causes. A goal of epidemiologic studies is to associate the risk of disease with exposure to an agent.

Methodologically, epidemiologic studies require accurate estimates of exposure and must be designed to have the power and sensitivity necessary to test the hypothesis. A number of inhalable agents such as tobacco smoke and other combustion mixtures, particulate matter, and oxidants have been implicated in the etiology or development of disease states in human populations.

Applications are requested for the epidemiological study of:

Cancer of All Sites

The relationship between exposure to complex mixtures and cancer is complex. Epidemiological research is needed to identify external and internal risk factors for the development of cancer of all sites as well as to characterize the independence or confounding potential of factors operating within complex multi-path biological systems.

Cardiovascular Diseases

Cardiovascular disease (CVD) represents the largest, single contribution to morbidity and mortality in developed countries. CVD includes but is not limited to coronary artery disease, ischemic heart disease, and stroke. Epidemiological research continues to identify external and internal risk factors among which are obesity, smok-

ing, hemodynamic flow, increased lipids, serum cholesterol, and proinflammatory processes leading to CVD with atherosclerosis as a common pathological feature.

Respiratory Diseases, Including Asthma and Chronic Obstructive Pulmonary Disease (COPD)

Results of recent epidemiological studies of outdoor exposures to complex mixtures have been consistent with chamber studies and suggest that vapor phase constituents of the mixtures may play a significant role in the development or exacerbation of respiratory symptoms as well as the coarse and fine fractions of particulate matter.

Reproductive, Maternal, and Placental Effects

Exposures to complex mixtures such as tobacco smoke have been implicated in the causation of reproductive and developmental health effects such as low birth weight. Epidemiologic studies would contribute to understanding of the impact of complex exposures on reproductive health endpoints.

Combination study designs for some or all of the above diseases/health effects as well as single endpoint studies are requested with emphasis on exposure characterization, biomarker use, and identification of potential mechanisms.

Epidemiologic studies that utilize state-of-the-art techniques would serve to enhance understanding of these diseases and health effects, in particular, genetic and genomic approaches to the identification and correlation of genetic polymorphisms in the population that relate to susceptibility and severity of outcome.

Clinical and Model Systems Research

Applications are requested for clinical and model systems on:

Cancer

While cancer can develop in a number of sites associated with inhalation of tobacco smoke and other combustion mixtures, the most common site for primary carcinogenesis is the lung.

Investigations are requested to:

- Develop animal models for smoking and cancer of all sites.
- Discern mechanism(s) of cancer with respect to areas such as:
 - host susceptibility factors including genetic susceptibility,
 - adduct formation,

- AH-receptors,
 - oxidative stress,
 - cell cycle regulation genes,
 - molecular reactions related to cell regulation,
 - cellular processes,
- Identify and study relevant smoke constituents related to mechanisms.

Cardiovascular Disease

Coronary artery disease is responsible for 44% of mortality in the United States and causes 800,000 new myocardial infarctions per year. Hypotheses have been put forward in which environmental inhalation exposures to complex mixtures, particularly the ultrafine fraction of particulate matter, can promote coronary disease. For example, inhalation of the mixture can cause airway inflammation, leading to a systemic acute phase response such as blood hypercoagulability, which then promotes a coronary event. Paradigms for the promotion of cardiac responses after inhalation of particle or vapor phase constituents could involve 1) the autonomic nervous system whereby inflammation leads to changes in heart rate variability, 2) a direct effect whereby the presence of cytokines in cardiac muscle leads to vasoconstriction, plaque rupture, or occlusion, and 3) relevant to smoking, an indirect effect whereby circulating mononuclear cells become activated by pulmonary capillary endothelium, enter plaques and contribute to events leading to their rupture.

Proposals will be considered to study:

- Cellular, biochemical, and molecular mechanisms of atherosclerosis and other cardiovascular disease states,
- Relevant smoke constituents related to mechanisms of cardiovascular disease,
- Early blood and serum markers for processes contributing to cardiac events,
- Development of a repository for exposed tissue with which to conduct ongoing and future research.

Respiratory Diseases

The study of respiratory disease as a result of environmental inhalation exposures continues to be an area of importance. Included in the diseases of interest within this focus are tobacco related illnesses such as COPD (emphysema and chronic bronchitis), asthma, and pulmonary fibrosis.

A proposed basis for onset and progression of respiratory disease is the occurrence of inflammation leading to airway hyperreactivity and resultant lung injury. The components of lung injuries represent relevant topics for research on the development of respiratory disease as the result of particle/vapor/complex mixture inhalation exposures including:

- Mechanisms of airway inflammation involving cytokines and lipids,
- Mechanisms of airway hyperresponsiveness,
- Epithelial damage and end-organ dysfunction,
- Susceptibility to microorganisms,
- Identification and study of relevant smoke constituents related to mechanisms.

Complex interactions occur during the development of lung injury. In asthma, for instance, the combination of airway inflammation and airway remodeling leads to airway obstruction. Airway remodeling is a complex sequence of events involving fibroblast activation, matrix protein synthesis, muscle hyperplasia, subepithelial fibrosis, and growth factor elaboration. The severity of resultant airway obstruction varies among the affected population.

Research applications are requested to:

- Ascertain the role of genetic factors in the production of airway inflammation and airway remodeling.
- Investigate the mechanistic role of environmental inhalation exposures as triggers of lung disease.
- Investigate host susceptibility factors in the etiology of lung disease due to environmental inhalation exposures.

With respect to loss of lung function as a measure of lung injury, the nonsmoking population as well as 85% of the smoking population exhibit virtually the same rate of decline of lung function with aging. An increased rate of decline of lung function is observed in

15% of the smoking population. However, if smoking is discontinued prior to apparent disability within the latter group, the rate of lung function loss returns to virtually the normal rate.

Research applications are requested to:

- Determine susceptibility factors that are responsible for accelerated loss of lung function.
- Investigate what role inflammation plays in the predisposition to accelerated lung function decline.

For the study of all facets of respiratory disease, good model systems including assays and validation are needed so that results can be extrapolated reliably to humans. Currently, an animal model for the lung conductive airways is nonexistent because humans have very different airway branching and deposition patterns from traditional laboratory animal models used to study disease.

Research applications are requested to:

- Develop animal models for lung disease, including assays and validation.

Reproductive, Maternal, and Placental Effects

Applications are requested to:

- Develop clinical and model systems for the study of reproductive, maternal, and placental effects of inhalation exposures.
- Investigate effects of inhalation exposures on reproductive and developmental health.
- Ascertain relevant smoke constituents related to mechanisms.

Studies that utilize state-of-the-art techniques would serve to enhance understanding of these diseases and health effects, in particular, molecular and genomic approaches to gene networks associated with normal vs. disease states in the affected tissues and analytical approaches to extracting relevant targets and principles from such data.

Tobacco Smoke and Smoking Behavior

Research applications are requested to investigate the relationship of smoking behavior to:

- The role of nicotine and/or other substances as determinants of smoke exposure.

- Dosimetry of nicotine and other smoke constituents with respect to bioavailability and biokinetics.
- Effects of smoke constituents on sensory systems.
- Operative biochemical and molecular mechanisms involving tobacco smoke constituents.
- Brain activity measured differentially with modern imaging techniques, in order to understand neural processes occurring before, during and after smoking.
- Studies are requested to characterize pharmacologically active constituents of tobacco smoke other than (S)-nicotine and to enhance understanding of the pharmacologic impact of these constituents on effects such as dependence and cognition.